#15

Patent
Attorney's Docket No. 010091-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Richard SCHLEGEL et al.	)	Group Art Unit: 1813
	)	
Application No.: 08/216,506	)	Examiner: A. Caputa
	)	
Filed: March 22, 1994	)	
	)	
For: PAPILLOMAVIRUS VACCINE	)	

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

(1) I, Jeffrey Cossman, M.D., declare and state that I am a citizen of the United States.

(2) I was awarded a M.D. from the University of Michigan Medical School in 1973. I have been employed by Georgetown University School of Medicine as a Professor and Chairman of the Department of Pathology from 1989 to date. I am an expert in hematopathology and immunology. My curriculum vitae is attached to this declaration.

(3) I have reviewed U.S. Patent Application No. 07/903,109 filed on June 25, 1992 by Richard Schlegel and Bennett A. Jenson entitled "Papillomavirus Vaccine", and now refiled as U.S. Serial No. 08/216,506 on March 22, 1994. I have further reviewed the prosecution history in connection with the 07/903,109 application, and in particular the Official Action issued on September 22, 1993.

(4) Based on my review of the Official Action issued by Examiner Caputa on September 22, 1993, it is my understanding that the Examiner remains of the opinion that the patent application does not establish that conformationally correct papillomavirus L1 proteins may be used as vaccines against papillomaviruses. I have been advised that for patent claims to be patentable, that the application must enable one skilled in the art to practice the claimed invention, the claimed invention must comprise a patentable utility, and the invention must be novel and non-obvious to one skilled in the art.

(5) I disagree with the Examiner's conclusion that the patent application does not establish that conformationally correct L1 proteins comprise utility as papillomavirus vaccine compositions, and further with the Examiner's conclusion that the application does not enable the use of conformationally correct L1 proteins as vaccines for conferring immunity against papillomavirus infection. I am of the opinion that the *in vitro* evidence contained in the present application provides convincing evidence that conformationally correct L1 proteins may be used as effective papillomavirus vaccines.

(6) As an expert in the art, I can well attest to the fact that the two *in vitro* assays disclosed in the present application which were used to test the efficacy of conformationally correct L1 and L2 proteins as immunogenic compositions, specifically the xenograft neutralization assay and the C127 cell neutralization assay, comprise well established, art recognized, patented assays (xenograft) for evaluating the neutralization of papillomaviruses by putative immunizing compositions. I further

disagree with the Examiner's conclusion that these assays would not be regarded to be adequately predictive of the *in vivo* utility of conformationally correct L1 proteins for affording protection against papillomavirus infection by those skilled in the art. Therefore, it is my expert opinion that the fact that antibodies against conformationally correct L1 are disclosed in the patent application to be neutralizing in two different art recognized assays provides convincing evidence that conformationally correct L1 proteins will confer protection when administered *in vivo* to susceptible hosts.

(7) I further disagree with the Examiner's assertion that the observation that some human sera and mouse monoclonal antibodies which react with intact BPV-1 particles, but do not to prevent HPV-induced cyst formation in the nude mouse assay, is evidence that conformationally correct L1 proteins are non-protective. As an expert in the art, I can attest to the fact that it is well known that papillomaviruses are closely related and can share antigenic epitopes, including surface epitopes. Most importantly, it is critical to realize that there are two forms of conformational epitopes on the papillomavirus surface: neutralizing and non-neutralizing. Hence, it is not surprising that some human sera might contain antibodies which cross-react with conformational epitopes of BPV-1 but would not necessarily neutralize BPV-1. Humans are not infected with or vaccinated against conformationally correct BPV-1 capsid proteins and would not be anticipated to generate neutralizing antibody responses. I further do not find it surprising that not all mouse monoclonal antibodies reactive with intact BPV-1 particles neutralize BPV-1. In a previous study with HPV-11, it has been clearly shown

that mice can generate monoclonal antibody responses which are either protective or non-protective, depending upon whether they recognize neutralizing or non-neutralizing epitopes. It is also critical to note that conformationally incorrect proteins did not produce neutralizing antibodies in this same study.

(8) I also do not believe that the results with human antisera refute the predictiveness of the xenograft and C127 viral neutralization assays. Rather, these results merely highlight the importance for defining the relevant conformational epitopes on the virus surface. The xenograft and C127 neutralization assays are valid assays, however, the human and mouse monoclonal antibodies simply did not contain antibodies generated against neutralizing epitopes.

(9) I further disagree with the Examiner's assertion that the application does not adequately establish that the antibody response to conformationally correct capsid proteins will be sufficient to confer protection *in vivo*. As discussed *supra*, I can attest to the fact that the two disclosed *in vitro* assays are accepted in the art, and comprise the best known *in vitro* models for evaluating the efficacy of putative papillomavirus immunogens.

(10) I further strenuously disagree with the Examiner's assertion that the NIH grant awarded to Richard Schlegel provides evidence that these *in vitro* assays are not acceptable evidence for establishing the utility of the claimed vaccine. The comments in the grant relating to the use of a canine animal model emphasize the importance of using a relevant in-vivo model for evaluating the efficacy of any potential human

papillomavirus vaccine. However, notwithstanding the superiority of this in-vivo model, this does not refute the efficacy of either the in-vitro models of the xenograft neutralization assay or the C127 cell neutralization assay which are art recognized models for the study of papillomavirus infection.

(11) While I am of the opinion that the disclosed *in vitro* evidence contained in the application is sufficient to establish that recombinant, conformationally correct L1 proteins may be used as effective papillomavirus vaccines, I believe that the data contained in the Schlegel § 132 Declaration submitted herewith provides incontrovertible evidence which refutes the Examiner's assertion that the invention lacks utility. In particular, the data contained in the Schlegel §132 Declaration provides convincing *in vivo* evidence that recombinant conformationally correct COPV-1 L1 proteins when administered to beagle dogs confer immunity upon challenge with infectious COPV. Given the high level of similarity between COPV and HPV-1, I am of the opinion that this provides convincing evidence that recombinant conformationally correct HPV L1 proteins may be used to confer immunity against homologous HPV infection. I further support my opinion based on the fact that an FDA official has stated to one of the present inventors, Bennett A. Jenson, that the FDA would consider the canine data contained in the Schlegel Declaration to comprise acceptable *in vivo* evidence for providing the efficacy of conformationally correct HPV L1 protein vaccine compositions for use in humans.

(12) I am further of the opinion that it would not require undue further experimentation for the ordinary skilled artisan to clone and express the L1 protein from any known papillomaviruses and to use same as a vaccine composition against the corresponding papillomaviruses given the teachings in the application and what had been known in the art at the time of the invention. In this regard, the L1 genes from a large number of papillomaviruses have been cloned and sequenced prior to the invention and were known to comprise substantial sequence homology. Additionally, L1 proteins of papillomaviruses are structurally and functionally related in that these proteins always comprise the major capsid protein which is expressed on the surface of a particular papillomavirus. Hence, based on the results obtained with both BPV-1 and COPV-1 L1 proteins, I would similarly expect that L1 proteins from other papillomaviruses could be expressed in conformationally correct form in eukaryotic host cells and be used as effective vaccines against a papillomavirus strain which expresses that particular L1 protein.

(13) I further understand the Official Action to assert that it would have been obvious based on the Christensen et al, Pilacinski et al, Sambrook et al and Danos et al references to express a papillomavirus L1 protein in a eukaryotic host cell in conformationally correct form and to use the resultant conformationally correct L1 proteins as immunogens to confer immunity against papillomavirus infection. I have reviewed all of these references in relation to the claimed invention. I disagree with the

Examiner's conclusion that the claimed outcome was obvious based on these references.

As an expert in the art, I can attest to the fact there is a high level of unpredictability associated with expressing viral proteins in native conformationally correct form, i.e., the form that the protein assumes when it is expressed on the surface of the infectious virus. As an expert in immunology, I can further attest to the fact that there is a very high level of unpredictability associated with producing and identifying viral proteins which may be used as protective immunogens. Given this high level of unpredictability, it could not have been predicted based on any of the cited references, whether considered singularly or in combination, that L1 proteins, even if expressed in conformationally correct form, would be sufficiently immunogenic to confer immunity against papillomavirus in a susceptible host. For example, immunization to papillomavirus may have required viral proteins other than the L1 protein, e.g., the L2 protein. Alternatively, the protein could have been expressed in a form such that not all of the necessary epitopes are presented to a host's immune system.

(14) The non-routine nature of the claimed invention is further established by the Summary Statement of experts in the art who were chosen by the USPHS to review the Schlegel grant proposal pertaining to the potential canine oral papillomavirus vaccine and its use as an *in vivo* model for evaluating the efficacy of human papillomavirus vaccines. In particular, while the reviewers state that in their expert

opinion the canine model would appear to be the best available *in vivo* model for evaluating HPV immunogens, they expressed their collective opinion that eukaryotic cells (COS cells or Sf9 cells) might not be able to express COPV-1 L1 proteins which stimulate a sufficiently strong neutralizing antibody response to COPV. Thus, contrary to the Official Action, experts in the art were not of the opinion that the claimed invention was of a routine nature, and therefore awarded the grant with the highest priority to test the hypothesis.

(15) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 6-10-94

Jeffrey Cossman, M.D.

CURRICULUM VITAE

Jeffrey Cossman, M.D.

November 10, 1993

Date and Place of Birth: November 1, 1947; Flint, Michigan

Marital Status: Married to Wendy S. Cossman
children: Jenna 3/24/87; Allison 6/29/90

Citizenship: United States

Social Security No.: 365-48-5734

Home Address: 932 Willowleaf Way
Rockville, MD 20854

Education:

1965-1969, University of Michigan, B.S. 1969
1969-1973, University of Michigan Medical School, M.D. 1973

Postgraduate Training and Experience:

1973-1974, Pathology internship, Stanford University
1974-1977, Pathology residency, University of Michigan
1977-1979, Fellowship, Hematopathology Section, NCI, NIH

Licensure/Board Certification:

Licensed (0101040269) to practice medicine in the State of Virginia
Licensed (D33143) to practice medicine in the State of Maryland
Licensed (35326) to practice medicine in the State of Michigan
Licensed (18080) to practice medicine in the District of Columbia
Diplomate of American Board of Pathology, Anatomic Pathology (June 1977)

Chronology of Employment (most recent first):

Professor and Chairman, Department of Pathology, Georgetown University School of Medicine, 1989 - present

Senior Investigator, Laboratory of Pathology, NCI, NIH, 1979-1989

Pathologist, Laboratory of Pathology, NCI, NIH, 1977-1979 (concurrent joint faculty appointment, Instructor, Department of Pathology, University of Michigan)

Military Service:

Commissioned Officer, U.S. Public Health Service, July 1981 - July 1988 (honarable discharge at O5 grade)

Memberships in Societies:

American Society of Hematology
International Academy of Pathology
American Federation of Clinical Research
American Association of Pathologists
Hematopathology Society
Washington Society of Pathologists
Association of Pathology Chairmen
College of American Pathologists
American Association of Cancer Research
Peripatetic Club
Cosmos Club

Editorial Board Appointments:

Hematologic Pathology - Associate Editor
American Journal of Pathology - Associate Editor
Cancer Research - Associate Editor
Hematological Oncology - Associate Editor
Diagnostic Molecular Pathology - Associate Editor
Atlas of Tumor Pathology - Editorial Advisory Board
Diagnostic Molecular Pathology - Editorial Board
Human Pathology - Editorial Board

Journal Reviewer:

Science
Blood
New England Journal of Medicine
Laboratory Investigation
Journal of the National Cancer Institute
Journal of Immunology
Cancer

Hematologic Pathology
American Journal of Pathology
Journal of Clinical Oncology
American Journal of Clinical Pathology
American Journal of Respiratory Disease
Cancer Research
Annals of Internal Medicine

Grant Reviewer:

NIH Program Project Grant Study Section (NCI), 1986
NCI Pathology Study Section A- ad hoc, 1989
NCI Pathology Study Section B- ad hoc, 1988
U.S. Veterans Administration, 1988
Medical Research Council (Canada), 1987-90
NCI Metabolic Pathology Study Section - ad hoc, 1989
NCI Program Project - Special Review Committee, 1991
ACS- Drug Development, Hematology and Pathology Study Section Member 1993-

Sponsored Research:

ACS - J. Cossman, PI - "Molecular basis of Hodgkin's disease" 1991-93

FDA-RFA, Richard Hopkins, PI - "Evaluation of unstested cardiac valves in a chronic sheep model", 1991-93.

Leukemia Society of America, Sponsor, Special Fellow (Adam Bagg, M.D.), 1992-95.

MRC Canada, Sponsor, Fellowship (Ginette Michaud, M.D.) 1992-1995

NIH-CCSG, (Marc Lippman, MD, PI) Experimental Hematology Oncology Program, J. Cossman, Director, (pending)

ACS- Special Fellowship in Oncology (Hematopathology), J. Cossman, Sponsor, pending

Committees:

Georgetown University
Graduate School Executive Committee - Georgetown University, 1991
Faculty Practice Group, 1989-present
Executive Faculty, Georgetown University School of Medicine, 1989 - present
Executive Staff, Georgetown University Medical Center, 1989 - present
Cancer Task Force, Lombardi Center, Georgetown University, 1989-90
Basic Science Chairmen Committee, 1989 - present
Hematology/Oncology Program Task Force - Chairman, 1990-91
Committee on Faculty, 1990 - present
Physiology Review Committee, 1991
Chair, Search Committee for Chairman of Department of Physiology, 1991
Breast Cancer SPORE Executive Committee
Select Committee of the Dean for Research, 1991

National
Southwest Oncology Group (SWOG) Lymphoma Repository, Molecular Consultant, 1991-current
Jonathan Rhoads Awards Committee, American Association of Cancer Research, 1991
Intersociety Committee on Pathology Information, Representative of the American Association of Pathologists, 1991-94
Scientific Advisory Board- Armed Forces Institute of Pathology 1991-current
Education Committee - American Association of Pathologists, 1991-current
John Hill Brinton Award Committee - Armed Forces Institute of Pathology - 1992
Research Committee of the Association of Pathology Chairmen, 1991-current

Awards:

National Science Foundation Student Fellowship - 1968

The University of Michigan Medical School Predoctoral Research fellowships: 1969, 1970 and 1972

1983 U.S. Public Health Service Commendation Medal

Awards (cont):

U.S.-Canadian International Academy of Pathology Recognition Award - 1986

1987 U.S. Public Health Service Outstanding Service Medal

Outstanding book on cancer for 1991, *Journal of the National Cancer Institute.*

Teaching Experience:

1968-1969, Biological Anthropology, University of Michigan
1973-1974, Medical School Pathology, Stanford University
1975-1977, Medical School Pathology, University of Michigan
1977-present, Pathology teaching of pathology residents and hematopathology fellows
1977 - present, Postgraduate lectures--hematopathology and molecular biology courses (see invited lectures)
1988-89, 75 hour hematopathology course, "Molecular Biology of the Normal and Neoplastic Immune System"
1989-present, Georgetown University: Second year pathology course: *Principles of cancer*, weekly hematopathology residents teaching, weekly molecular pathology course

Postdoctoral Fellows

at NIH:
Rita Braziel, M.D.
Edward Lipford, M.D.
Charles Simrell, M.D.
Mark Raffeld, M.D.
Rita Rizzi, M.D.
Stefania Pittaluga, M.D.
Rafael Andrade, M.D.
Robert Coupland, M.D.
Paul Cohen, M.D.
Micheal Uppenkamp, M.D.
Lori Elwood, M.D.
Maryalice Stetler-Stevenson, M.D., Ph.D.
Jeffrey Medeiros, M.D.
James Sundeen, M.D.

at Georgetown University
Adam Bagg, M.D.
Hiroshi Kamesaki, M.D.
Ginette Michaud, M.D.
Nicholas Sioutis, M.D.

Invited Lectures:

Continuing Pathology Seminar on Malignant Lymphomas, University of Michigan Medical School, December 1979
Histopathology of Cancer Workshop, Hematopathology Course, Lake Placid. New York, July 1980, October 1981
George Washington University School of Medicine, Department of Pathology, February 9, 1981
International Academy of Pathology, Faculty, "Malignant Lymphomas: Tumors of the Immune System." Annually, 1981-1986
University of Michigan Medical School, June 4, 1981
Hepatic Pathology Course, Armed Forces Institute of Pathology, Annually 1981-1983
George Washington University School of Medicine, Department of Pathology, October 19, 1981
Holy Cross Hospital, Ft. Lauderdale, Florida, January 4, 1982
First Annual Hematopathology Society Seminar, "Diversity of Immunologic Phenotypes of T Cell Lymphomas," Boston, Massachusetts, February 28, 1982
Hematopathology Slide Seminar, International Academy of Pathology, Boston, Massachusetts, March 2, 1982
University of Virginia School of Medicine, Charlottesville, Virginia, February 24, 1982
Walter Reed Medical Center, Department of Pathology, Washington, DC, March 18, 1982
Georgetown University School of Medicine, Department of Hematology, Washington, DC, April 22,1982
University of Colorado School of Medicine, Continuing Education Course, Denver, Colorado, April 30, 1982
International Workshop on the Influence of the Environment on Leukemia and Lymphoma Subtypes, NIH, May 5-6, 1982
Michigan Society of Pathology, featured speaker, Annual Meeting, Bay City, Michigan, May 1982
NIH-FAES Surgical Pathology Course, Bethesda, Maryland, Annually, 1982-1989
Annual Memphis Hematology Seminar, Memphis, Tennessee, September 1982
College of American Pathology, Flow Cytometry, Miami Beach, Florida, October 1982
Washington Hospital Center, Department of Pathology, Washington, DC, November 1982
George Washington University Medical School, Pathology Course, Washington, DC, 1982, 1983
Maryland-Washington Pathology Society, featured speaker, Annapolis, Maryland, September 1982
American Society for Hematology, Faculty, Educational Program, 1982-1984
U.S. Naval Hospital-Pathology, Bethesda, Maryland, February 1983
Flow Cytometry Workshop, Wilmington, Delaware, February 3, 1983
Hematopathology Slide Seminar, International Academy of Pathology, Boston, Massachusetts, March 1983
Holy Cross Hospital, Ft. Lauderdale, Florida, April 5, 1983

Invited Lectures (cont):

Washington Hospital Center, Clinical Oncology Grand Rounds, April 19, 1983
American Association for Clinical Chemistry, Washington Hospital Center, May 7, 1983
Henry Ford Hospital, Department of Pathology, Detroit, Michigan, May 13, 1983
University of Nebraska, Department of Pathology, Omaha, Nebraska, June 2, 1983
Bishop Clarkson Hospital, Faculty, Cancer Series, Omaha, Nebraska, June 3, 1983
Visiting Professor in Oncology, East Virginia Medical School, September 26-27, 1983
Tutorial on Neoplastic Hematopathology, Faculty, Duarte, California, October 31, 1983
Washington Hospital Center, Medical Grand Rounds, Washington, DC, February 14, 1984
American Cancer Society-Montgomery General Hospital, Oncology Series, Rockville,Maryland, March 10, 1984
International Academy of Pathology, Lymphoma Course, Miami Beach, Florida, September 4, 1984
Georgetown University, Hematology Grand Rounds, January 22, 1985
Walter Reed Medical Center, Department of Pathology, April 11, 1985
University of California at Irvine, Hematological Neoplasia, May 29-30, 1985
Pathology and Diagnosis of Early Neoplasia, "Early Development of Lymphoma," Waldorf, West Germany, October 9, 1985
Tutorial on Neoplastic Hematopathology, "Immunologic Identification of Normal and Neoplastic Lymphoid Cells," Pasadena, California, October 14, 1985
Update on Intensive Treatment Programs in Diffuse Large Cell Lymphoma, Miami, Florida, November 14-17, 1985
International Academy of Pathology, long course on Malignant Lymphoma and Leukemia, New Orleans, Louisiana, March 12, 1986
New Solutions to Old Problems in Surgical Pathology, FAES Conference, Rosslyn, Virginia, October 28, 1986
Combined Clinical Staff Conference, NIH, March 18, 1987
AFIP 11th Annual Course on Pathology of Lymph Nodes, April 29, 1987
Department of Pathology, Georgetown University School of Medicine, May 1, 1987
"Gene Rearrangements in Reed-Sternberg Cell Enriched Fractions of Hodgkin's Disease," Hodgkin's Disease: New Perspectives on Old Controversies in 1987, MD Anderson Hospital and Tumor Institute, Houston, TX May 29, 1987
"Molecular Genetic Tools for the Diagnosis of Lymphoma," FAES New Solutions to Old Problems in Surgical Pathology, October 7, 1987
"Gene Rearrangement in Human Lymphoma," AAP Concepts in Molecular Biology, Bethesda, MD 1987-1991
Department of Pathology, Georgetown University, January 29, 1988 "Applications of Molecular Genetics to the Diagnosis of Lymphoproliferative Disorders," Tutorial on Neoplastic Hematopathology, Los Angeles, California, February 8-12, 1988
Grand Rounds of Clinical Pathology, NIH, Bethesda, Maryland, April 21, 1988
Massachusetts General Hospital, Harvard University, Oncology Rounds, Boston, Massachusetts, May 4, 1988
Visiting Professor of Clinical Pathology, University of Michigan, Ann Arbor, Michigan, May 12-13, 1988
AFIP Course on the Pathology of Lymph Nodes, Bethesda, Maryland, May 24-27, 1988
"Diagnostic Application of Molecular Genetics to Hematopathology," American Society of Clinical Pathology, Chicago, Illinois, June 19, 1988

Invited Lectures (cont):

NIH Science Writers Seminar, Bethesda, Maryland, June 23, 1988
Pathology Rounds, Washington Hospital Center, Washington, DC, July 19, 1988
Grand Rounds, Washington Hospital Center, Washington, DC, October 4, 1988
International Symposium on Immunoregulatory Mechanisms and their Clinical Implications, Budapest, Hungary, November 20-21, 1988
Tutorial on Neoplastic Hematopathology, "Flow Cytometry" and "Applications of Molecular Genetics in the Diagnosis of Hematopoietic Disorders," Faculty, Los Angeles, California, February 6, 1989
"Molecular Genetics of Lymphoma," Fox Chase Cancer Center, Philadelphia, Pennsylvania, March 6, 1989
University of Pennsylvania, Visiting Professor of Pathology, Philadelphia, Pennsylvania, April 3-4, 1989
12th Annual AFIP Course on Lymph Node Pathology, "Molecular Genetics and the Diagnosis of Lymphoma," Washington, DC, May 9, 1989
AFIP Symposium on Diagnostic Immunology and Molecular Biology, "Molecular Genetics of Lymphoproliferative Disorders," Washington, DC, May 15, 1989
"Gene Rearrangement in Human Lymphoma", AAP Concepts in Molecular Biology, Washington, DC, October, 1989
AFIP Course on Immunopathology. "The Molecular Pathology of Lymph Nodes, Bethesda, MD, May, 1989
New Solutions to Old Problems in Surgical Pathology, FAES Course, Bethesda, MD, October, 1989
"Gene Rearrangements and the Diagnosis of Lymphoma", Kogod Memorial Lymphoma Symposium, Georgetown University, September, 1989
Grand Rounds - Clinical Laboratory, Georgetown University, December, 1989
Tutorial on Neoplastic Hematopathology, "Flow Cytometry" and "Applications of Molecular Genetics in the Diagnosis of Hematopoietic Disorders", Faculty, Orlando, Fla, February, 1990
Surgical Grand Rounds - Georgetown University, April, 1990
13th Annual AFIP Course on Lymph Node Pathology, "Molecular Genetics and the Diagnosis of Lymphoma", Washington, DC, May, 1990
AFIP Course on the Pathology of Lymph Nodes, Bethesda, MD, May, 1990
New Solutions to Old Problems in Surgical Pathology, FAES Course, Bethesda, MD, October, 1990
Medical Grand Rounds - Georgetown University, June 7, 1990
"*bcl*-2 Gene and the Pathogenesis of Lymphoma". Fidia-Georgetown Foundation for the Neurosciences, August 29, 1990.
"Gene Rearrangement in Human Lymphoma". AAP Concepts in Molecular Biology, Bethesda, MD, October, 1990
Tutorial on Neoplastic Hematopathology, Orlando, FL, February 4, 1991.
United States and Canadian Academy of Pathology, Society for Hematopathology Symposium on Reactive Lymphadenopathies: "AILD- Current Studies", Chicago, IL., March 17, 1991
United States and Canadian Academy of Pathology, Binford-Dammin Society for Infectious Disease Pathologists, Symposium, "Molecular Genetics of Reactive Lymphoproliferative Processes", Chicago, IL, March 17, 1991
Conference on Biotechnology for the Diagnosis of Genetic Disease, Arlington, VA, April, 1991

Invited Lectures (cont):

AFIP Hematopathology Course, Bethesda, MD, May, 1991
New Jersey/Pennsylvania Society of Pathologists, Hershey, PA, June, 1991
XVI World Congress of Anatomic and Clinical Pathology, "DNA Technology in the Diagnosis of Lymphoma", Vancouver, BC, June, 1991
2nd International Symposium on Hodgkin's Lymphoma, Cologne, Germany, October, 1991
AMA/Georgetown - Symposium on the Clnical Application of PCR, Washington, D.C., October 11, 1991
"Gene Rearrangement in Human Lymphoma". AAP Concepts in Molecular Biology, Bethesda, MD, November 2, 1991
United States and Canadian Academy of Pathology-Special Course "New Insights into Cancer Provided by Molecular and Cellular Biology", March 19, 1992
Hematopathology Tutorial, Orland, FL, February, 1992.
AFIP Hematopathology Course, May, 1992.
AFIP Invited Scientist Series, April, 1992.
Opening Address - Conference on Molecular Diagnostics - National Meeting of ASCP-CAP-APC, October 12, 1992. Las Vegas, Nevada.
NCI Early Detection of Ccancer. Bethesda, MD, Oct 29, 1992
ASIP Molecular Biology Course, Bethesda, MD, October 31, 1992.
National Naval Medical Center, Pathology Grand Rounds, Bethesda, MD, November 12, 1992

RESEARCH ACCOMPLISHMENTS

1. First demonstration that expression of rearranged immunoglobulin genes in precursor B cell leukemia (common ALL), follicular lymphoma and chronic lymphocytic leukemia could be induced *in vitro*.
2. First demonstration of clonal evolution of follicular lymphoma. Based on a novel approach for the production of monoclonal anti-idiotypic antibodies directed against follicular lymphoma.
3. Demonstration of a hierarchy of T cell receptor gene rearrangement, transcription and translation in a series of developmentally arrested neoplastic precursor T cell clones.
4. Development of clonal mutants of the precursor T cell line, CEM, and identification of Ta gene transcription as the limiting step regulating T cell receptor-T3 expression.
5. First demonstration of clonal expansion and regression of both B and T cell clones in a lymphoproliferative disorder (AILD).
6. Gene rearrangement analysis that revealed recurrent follicular lymphomas are not biclonal but result from growth of resistant cells. Despite lability of the immunoglobulin gene loci, the *bcl*-2-JH sequence resulting from t(14;18) translocation was conserved.
7. Demonstration of a method to analyze the diversity and selection of rearranged T-gamma variable region genes can be analyzed in a human immune response.
8. First demonstration of clonal immunoglobulin gene rearrangements in purified Reed-

Sternberg cells of Hodgkin's disease lymphocyte fractions depleted of Reed-Sternberg cells.

9. Detection of occult follicular lymphoma at a sensitivity 10^4 greater than conventional methods using amplification of t(14;18) sequences by polymerase chain reaction (PCR).
10. Rearrangement of the human T cell receptor delta gene prior to beta and gamma in early T cells. Discovery of a novel, second V-delta gene. Furthermore, the T-delta gene is frequently rearranged in human pre-B cell leukemias as a Vd_2-Vd_2-Dd_3 recombination.
11. First demonstration of the involvement of the *bcl*-2 oncogene in Hodgkin's disease.

BIBLIOGRAPHY

1. Frisancho, A.R. and Cossman, J.: Secular trends in infant mortality at high altitude. *Am. J. Phys. Anthropol.*, June 1969.

2. Kometani, K., Payne, P., Cossman, J., and Behrman, S.J.: Detection of antigens similar to placental antigens in mouse fertilized eggs by immunofluorescence. *Am. J. Obstet. Gynecol.* 116: 351, 1973.

3. Deegan, M.J., Cossman, J., Chosney, B.T., and Schnitzer, B.: Hairy cell leukemia: an immunologic and ultrastructural study. *Cancer* 38: 1952-1961, 1976.

4. Cossman, J., Deegan, M.J., and Schnitzer, B.: Complement receptor B lymphocytes in nodular sclerosing Hodgkin's disease. *Cancer* 39: 2166-2174, 1977.

5. Cossman, J., Schnitzer, B., and Deegan, M.J.: Immunologic surface markers in non-Hodgkin's lymphomas. *Am. J. Pathol.* 87: 19-32, 1977.

6. Cossman, J., Deegan, M.J., and Batsakis, J.G.: Warthin's tumor: evidence supporting a lymph node origin. *Arch. Pathol.* 101: 354-356, 1977.

7. Cossman, J., Glorioso, J.C., and Adler, R.: Complement receptors: specific detection by molecular complexes. *J. Immunol. Methods* 19: 227-234, 1978.

8. Cossman, J., Deegan, M.J., and Schnitzer, B.: Thymoma: an immunologic and electron microscopic study. *Cancer* 41: 2183-2191, 1978.

9. Cossman, J., Schnitzer, B., and Deegan, M.J.: Coexistence of two lymphomas with distinctive histologic, ultrastructural and immunologic features. *Am. J. Clin. Pathol.* 70: 409-415, 1978.

10. Adler, R., Glorioso, J.C., Cossman, J., and Levine, M.: Possible role of Fc receptors on cells infected and transformed by Herpes virus. Escape from immune cytolysis. *Infect. Immun.* 21: 442-447, 1978.

11. Cossman, J. and Berard, C.W.: Histopathology of childhood non-Hodgkin's lymphomas. *In* Graham-Pole, J. (ed.): *Non-Hodgkin's Lymphomas in Childhood.* Progress in Hematology - Oncology Series. Masson Publ., 1980, pp. 13-36.

12. Cossman, J. and Berard, C.W.: Malignant lymphomas: role of immunologic markers in diagnosis, classification and management. *Hum. Pathol.* 11: 309-311, 1980.

13. Azar, H.A., Jaffe, E.S., Berard, C.W., Callihan, T.R., Braylan, R.C., Cossman, J., and Triche, T.J.: Diffuse large cell lymphomas (reticulum cell sarcomas): correlation of morphological features with functional markers. *Cancer* 46: 1428-1441, 1980.

14. Berard, C.W., Cossman, J., and Jaffe, E.S.: Malignant lymphomas as tumors of the immune system. *Br. J. Cancer* 42: 1, 1980.

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